REMARKS

Claims 2-7, 10, 11, 16-26, 29-35, and 37-44 will remain in the application for further prosecution. New Claim 44 has been added to replace Claim 1, with Claims 2, 4, 5, 6, 7, 10, 11, 17, 18, 19 and 20 amended to correct their dependency. Claims 6, 7, 10, 11, and 21 have been amended to further distinguish the present invention from the cited references, which are discussed below. Claims 1, 8, 9, 27 and 28 have been cancelled.

Rejections Under 35 U.S.C. 112

Claims 1-11, 16-35, and 37-43 have been rejected under the first paragraph of 35 U.S.C. 112. The Examiner contends that the specification does not support the term "predetermined fixed liquid volume". This rejection may have been rendered moot in view of the replacement of Claim 1 with Claim 44.

The Applicants' method requires that it is carried out within a device having defined physical parameters and inherently operated in a batch manner. Fixed volumes of liquid contained in wells are transferred to chambers for mixing, the chambers being larger than the combined volume of the wells.

When such predetermined volumes are combined and mixed in subsequent chambers, the volume of chambers is defined with respect to the predetermined volumes of the wells supplying the chambers. Accordingly, in Claims 6 and 7 the first and second chambers have volumes at least about twice that of the combined predetermined liquid volumes. In claims 10 and 11 at least 100 μm is provided above the combined liquid level. Given a predetermined volume of the sample and reagent liquids, it is possible to determine the size and dimensions of the mixing chambers.

From the Examiner's response to arguments on page 9 of the office action, and from his previous emphasis on the Koop patent, it appears that the principal disagreement is on whether the Applicants' microfluidic device inherently operates in a batch mode, or whether the claims could be construed to include continuous operation. We believe that no specific structure is needed to demonstrate that the Applicants' device inherently is operated in a batch manner. The device is intended to receive a fixed amount of liquid sample and then process it to measure the amount of an analyte in the sample. Thus, all the mixing of the sample with other liquids, i.e. reagents and the like, is intended to produce reactions with the sample that can be measured. Those measurements must be related to the fixed amount of the sample and consequently the device must operate in a batch manner. All of the figures and the examples support such an understanding. Notice Example 1, where a fixed (predetermined) volume (10uL) of a liquid was added to sample well 10. Well 14 was filled with 10uL of another liquid. The two liquids were sent at the same time to first Chamber 18 having a volume of 36 μL, then to Chamber 22 having a capacity of 26 μL.

Furthermore, since the 1st and 2nd chambers have greater volumes than the combined volume of the wells receive the liquids to be mixed, space will remain in the 1st and 2nd chambers after they have received the mixed liquids. However, if liquids are added to the wells after they are filled, which is required by continuous operation, then the 1st and 2nd chambers will be filled and overflow. There will be no space for mixing of the liquids, which the claims require. Therefore, batch operation is inherent in both the method and the device claims and continuous operation is excluded.

Claims 6-20 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner contends that further method language is needed. The Applicants have previously (see the amendment of 5/19/06) pointed out that the structural features of claims 6-20 inherently are part of the method of the invention. Claims 6, 7, 10, and 11 have been amended to clarify the point. Claims 8 and 9 have been cancelled. Claims 16-20 should not be considered indefinite since they each refer to the method of mixing of liquids and are not just structural features.

Claims 25-28, 29-30, and 36 also have been rejected as indefinite. These are microfluidic device claims, that is, they define the volume of the first and second chambers (claims 25, 26, 29, 30) with relation to the volumes of the first and second liquid wells of Claim 21. Claim 36 is merely an alternative structure inherently within Claim 21. The Examiner contends that the volumes are related to the operation of the device and cannot be determined. However, the volumes of the device are related to the volumes used in operation and can be determined because the device inherently operates in a batch manner. As was pointed out above, the examples clearly indicate that the microfluidic devices being claimed mixed predetermined volumes of liquids as defined by the volume of the wells from which they are supplied.

Rejections Under 35 U.S.C. 103

Claims 1-4, 6-11, 16, 18-35, 37-38, and 42-43 have been rejected under 35 U.S.C. 103(a) as unpatentable (i.e. obvious) over Kellogg, et al (US 6,063,589) in view of Koop, et al (US 6,457,854). The Examiner implies that Kellogg has been previously cited, but, he has relied on Koop throughout prosecution of this application. The Applicants continue to believe that Koop's device operates in a continuous mixing mode and is therefore not relevant to their microfluidic

device which inherently operates with predetermined liquid volumes, i.e. it is a batch operated device. The Examiner's response to the Applicant's argument makes it clear that, despite the description and examples, he continues to believe that the device could be operated continuously. By now citing Kellogg, however, the Examiner appears to recognize that batch operation could have been intended.

Kellogg does disclose a batch operation operated by centrifugal force, that is by spinning the disc containing the liquids. Kellogg measures two liquids in a series of capillaries 602 and then discharges them by centrifugal force, where they join and pass through a mixing chamber 605 (see Example 5, column, 45). Kellogg states in column 46, lines 11-14 that "fluid flow within mixing chamber 605 was turbulent, in contrast to fluid flow through capillary barrier 603 or channel 604, which was primarily laminar, so that mixing occurred predominantly in mixing chamber 65." (emphasis supplied).

The mixing chamber 605 is clearly smaller than the volume of the combined liquids, as also is the receiving chamber 606. Therefore, Kellogg does not teach essential features of the Applicant's invention, which includes no mixing chamber and uses chambers of larger volume than the liquids being mixed. Fig. 14 is somewhat misleading. As described more definitely at column 45, the following sizes can be determined.

	Volume, μL	Dimensions
Metering array 602	25 μL each	0.5 x 0.5 x 16.6 x 6 = 25 $(mm)^3$ = 25 μL Col. 45, line 24
Mixing chamber 605	3 μL	0.75 x 2 x 2 = 3 $(mm)^3$ = 3 μL Col 45, lines 42-43

Receiving chamber 606	18.75 μL	5 x 5 x 0.75 = 18.75 $(mm)^3$ = 18.75 μL Col. 45, lines 62-63

These features were placed so that the centrifugal force on the liquids increased by the square of the instance from the center. Thus, the liquids were driven to greater speeds as they moved outwardly from the entry ports 601. It follows that this acceleration must have been involved in the mixing, since the volumes of both the mixing chamber 605 and the receiving chamber were smaller than the volume of either of the metering arrays. Therefore, Kellogg teaches a mixing system that is clearly not the same as that of the Applicants. Furthermore, there is no evident reason why one skilled in the art would conclude from Kellogg that the Applicant's method and device would provide satisfactory mixing. The difference between the device of Kellogg and that of the Applicants is not merely a matter of modifying volumes and dimensions to optimize results. One skilled in the art would assume that Kellogg had already done that and arrived at a different design consistent with his centrifugally driven platform.

Koop teaches a continuous mixing system which does not involve combining predetermined volumes of liquids by moving them into chambers which have volumes greater than that of the combined liquids. Therefore, Koop does not overcome the deficiency of Kellogg.

Claims 5, 17, 37, 39, and 41 have been rejected under 35 U.S.C. 103(a) as unpatentable over Kellogg in view of Koop and further in view of Nakajima et al (Nakajima). The deficiencies of Kellogg/Koop have already been discussed. Nakajima described an improved device to create emulsions from a dispersed phase and a continuous phase, which emulsions contain microspheres. The Nakajima device employs structures that are far different from those

of the Applicants' device. The Examiner relies on "obvious to one skilled in the art" to combine Nakajima with Koop. However, there is no suggestion anywhere that combining Nakajima with Koop would yield the Applicants' invention. Furthermore, neither Kellogg nor Koop nor the present invention involve forming emulsions. Consequently, Nakajima is non-analogous art.

In view of the amendments and the above remarks, the claims are believed to be in condition for allowance. If further amendment is believed necessary, the Examiner is invited to contact the Applicants' attorney, at the telephone number provided below.

Respectfully submitted,

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Date

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